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THYROID CANCER INCIDENCE AND MORTALITY TRENDS IN CROATIA 1988-2010

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SUMMARY – The aim of our study was to describe and interpret national trends in thyroid cancer in Croatian men and women during the 1988-2010 period, to better understand the incidence and mortality trends in comparison with other populations, and to determine the proportion of certain histologic subtypes of thyroid cancer and their impact on these trends. Using information from the Croatian National Cancer Registry and WHO Mortality Database, we estimated trends in the age-standardized incidence and mortality rates by joinpoint regression analysis. Thyroid cancer incidence increased in both women and men during the study period, with the estimated annual percent change (EAPC) of 6.4% and 5.5%, with no joinpoints identified. A significant decrease in mortality (EAPC -2.1%) was observed in women, while in men mortality rates decreased nonsignificantly (EAPC -1.3%). A statistically significant incidence increase was observed only for papillary carcinomas with annual incidence increase by 6.7% for women and 7.9% for men. During the study period, thyroid cancer showed an incidence increase in Croatia with persistent and steady decrease in mortality in women and statistically nonsignificant decrease in mortality in men. The increase in papillary carcinomas led to the thyroid cancer incidence increase and also affected the thyroid cancer mortality decrease in women. The trends observed are similar to those in other European countries and require additional analysis to determine all factors that have an effect on them.

Key words: *Thyroid neoplasms – epidemiology; Thyroid neoplasms – trends; Croatia*

Introduction

Thyroid cancer is the most common malignant disease of the endocrine system[1,2], making thyroid gland the ninth most common site of all cancers in women in the world and in Europe[3,4]. According to the EUCAN estimates for 2012, there were around 53 000 new cases and more than 6000 deaths from thyroid cancer in Europe, with women accounting for 77% of all new cases and 67% of deaths[4]. The trends observed are in favor of an increase in thyroid cancer incidence and a decrease in mortality[5-8]. In the US, thyroid cancer is the fastest increasing cancer in both sexes[2]. The risk factors for thyroid cancer are exposure to ionizing radiation, especially in childhood, having a history of goiter or thyroid nodules, family history of thyroid cancer, radioactive exposure, certain rare genetic syndromes, and female gender[2,9-11].

Changes in thyroid cancer incidence trends in particular countries have so far been associated with better medical diagnosis[5] and were attributed to the increase of papillary carcinomas[5,11], although not all changes could be explained so [12].

The aim of this study was to describe and interpret trends in the incidence and mortality of thyroid cancer in Croatian men and women during the 1988-2010 period, to compare them with trends in other

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populations and to identify possible changes, as well as to determine the proportion of certain histologic subtypes of thyroid cancer and their impact on the incidence trends in the Croatian population.

Methods

Data sources

Thyroid cancer has been defined in the International Classification of Diseases as ICD-9 code 193 and ICD-10 code C73[13]. Incidence data for the study period were obtained from the Croatian National Cancer Registry that includes the entire Croatian population (approximately 4.4 million persons)[14]. Data are collected as mandatory cancer notifications from primary and secondary health care sources and death certificates from the Croatian Bureau of Statistics[14]. The Registry has contributed data to the last three volumes of the Cancer Incidence in Five Continents series[15-17]. The numbers of cancer deaths were obtained from the WHO mortality database[18]. For calculating age-specific rates we used the United Nations population estimates[19].

Data on histologic subtypes were available in the Croatian National Cancer Registry for the period from 1998 to 2010. Histologic subtype diagnosis was available in 94.5% of cases in this period and it was coded using the International Classification of Diseases for Oncology, third edition (ICD-O-3)[20]. To further analyze the impact of each histologic diagnosis on the incidence trends in our study, thyroid cancer was divided into three groups: papillary carcinoma (ICD-O-3 codes 8050, 8052, 8260, 8340), follicular carcinoma (ICD-O-3 codes 8290, 8330, 8331, 8332), and others. For these three histologic subgroups, age-specific rates were calculated and used in further statistical analysis. Data on tumor size could not be obtained from the Croatian National Cancer Registry.

Statistical analysis

Age-standardized rates (ASR) and truncated ASR (for ages 30-64) of cancer incidence in Croatia were calculated by the direct standardization method using the world standard population as a reference[21]. To describe the incidence and mortality trends by calendar period, we carried out joinpoint regression analysis using the Joinpoint Regression Program, Version 4.0.4., May 2013[22]. The analysis included logarithmic transformation of the rates, standard error, maximum number of five joinpoints, and minimum of four years between two joinpoints. All other program parameters were set to default values. The aim of this approach is to identify possible joinpoints, where a significant change in the trend occurs. The method identifies joinpoints based on regression models with 0-5 joinpoints. The final model selected was the most parsimonious of these, with the estimated annual percent change (EAPC) based on the trend within each segment[23]. The same approach was used to calculate incidence trends of ASR for three histologic groups (papillary, follicular and others) in the 1998 to 2010 period. Joinpoint regression analysis was also used to calculate incidence trends for age-specific rates of ten-year age groups (30-39, 40-49, 50-59, 60-69, 70-79 and >80 years).

On describing trends, the terms "significant increase" or "significant decrease" denote that the slope of the trend was statistically significant ($p<0.05$). For statistically nonsignificant trends ($p>0.05$), we used the terms "stable" (for EAPC between -0.5% and 0.5%), "statistically nonsignificant increase" (for EAPC>0.5%), and "statistically nonsignificant decrease" (for EAPC <-0.5%). All statistical tests were two-sided.

Results

From 1988 to 2010, thyroid cancer was diagnosed in 5453 women and 1355 men (female-to-male ratio, 4 to 1), while 542 women and 282 men died from this malignant disease (female-to-male ratio, 2 to 1). The median age at diagnosis could have been calculated only for the 1998-2010 period. We compared two three-year periods; in the first period (1998-2000), median age at diagnosis was 50 years, with interquartile range of 40-62 years, and for the 2008-2010 period, median age at diagnosis was 52 years, with interquartile range of 39-62 years.

Women

In women, the number of new cases ranged from 99 to 409 annually in the study period, with the significantly increasing trend, EAPC of 6.4% (95% con-

Table 1. Thyroid cancer incidence and mortality in Croatian women 1988-2010

	Incidence			Mortality		
Year	N	Crude rate	ASRW*	N	Crude rate	ASRW*
1988	133	5.7	4.5	28	1.2	0.7
1989	119	5.1	4.1	23	1.0	0.5
1990	144	6.2	4.7	29	1.2	0.7
1991	111	4.7	3.7	20	0.9	0.4
1992	99	4.2	3.1	25	1.1	0.6
1993	164	6.8	5.0	27	1.1	0.5
1994	123	5.1	3.8	26	1.1	0.6
1995	179	7.4	5.7	16	0.7	0.3
1996	166	6.9	5.4	24	1.0	0.5
1997	172	7.2	5.4	18	0.8	0.4
1998	184	7.7	5.8	30	1.7	0.6
1999	261	11.1	8.5	26	1.1	0.5
2000	253	10.8	8.3	19	0.8	0.5
2001	258	11.1	8.1	15	0.6	0.2
2002	268	11.6	8.6	25	1.1	0.4
2003	282	12.2	9.1	25	1.1	0.5
2004	293	12.7	9.4	22	0.9	0.4
2005	331	14.4	10.2	22	1.0	0.4
2006	325	14.1	10.3	27	1.2	0.5
2007	374	16.3	11.8	17	0.7	0.4
2008	403	17.6	12.8	32	1.4	0.6
2009	402	17.6	13.2	22	1.0	0.3
2010	409	17.9	13.2	24	1.1	0.4

*ASRW = age-standardized rate *per* 100 000 (using world standard population)

fidence interval [CI], 5.5 to 7.2), with no joinpoints identified (Tables 1 and 2, Fig. 1). Significant increasing trends in the incidence were observed in all 30-79 age groups, with the most prominent increase (EAPC 10%) in the 50-59 age-group (Table 2). A significant decrease in mortality (EAPC -2.1%, 95% CI, -3.6 to -0.6) was observed in women in general; however, there was no significant change in age-specific mortality trends (Table 2).

Men

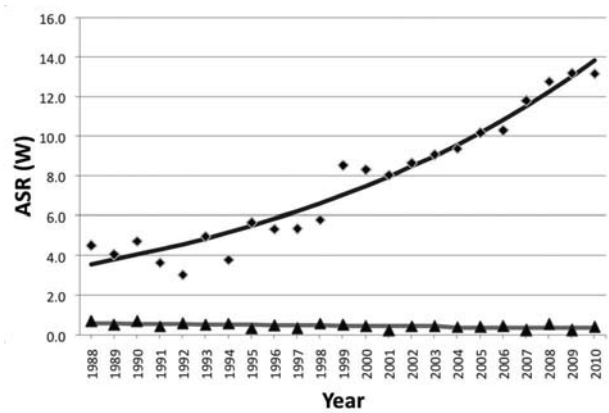
In men, the number of new cases ranged from 23 to 114 annually, with the significantly increasing EAPC

Table 2. Joinpoint analysis of age-specific and age-standardized rates of thyroid cancer incidence and mortality in Croatian women 1988-2010

Age (years)	Trend	
	years	EAPC† (%95 CI)
Incidence		
30-39	1988-2010	6.3* (4.7 to 8.0)
40-49	1988-2010	4.7* (3.0 to 6.5)
50-59	1988-2010	10.0* (8.1 to 11.9)
60-69	1988-2010	7.0* (5.4 to 8.7)
70-79	1988-2010	4.6* (2.8 to 6.4)
>80	1988-2010	-0.5 (-3.0 to 2.1)
Age-standardized		
overall	1988-2010	6.4* (5.5 to 7.2)
truncated (30-64)	1988-2010	6.4* (5.5 to 7.4)
Mortality		
30-39	1988-2010	N/A
40-49	1988-2010	N/A
50-59	1988-2010	N/A
60-69	1988-2010	-2.6 (-5.6 to 0.4)
70-79	1988-2010	-2.3 (-4.4 to 0.0)
>80	1988-2010	-0.5 (-3.0 to 2.1)
Age-standardized		
overall	1988-2010	-2.1* (-3.6 to -0.6)
truncated (30-64)	1988-2010	N/A

N/A = not applicable due to insufficient number of cases; *statistically significant trend; †EAPC = estimated annual percent change

Fig. 1. Joinpoint analysis of thyroid cancer incidence and mortality in Croatian women 1988-2010.



Rhomb = incidence; triangle = mortality; ASR(W) = age-standardized rate *per* 100 000 (using world standard population)

Table 3. Thyroid cancer incidence and mortality in Croatian men 1988-2010

	Incidence			Mortality		
Year	N	Crude rate	ASRW*	N	Crude rate	ASRW*
1988	42	1.9	1.9	21	1.0	0.7
1989	23	1.1	0.9	13	0.6	0.5
1990	35	1.6	1.2	8	0.4	0.3
1991	29	1.3	1.1	11	0.5	0.4
1992	27	1.2	1.0	8	0.4	0.2
1993	40	1.8	1.5	10	0.5	0.3
1994	32	1.4	1.2	9	0.4	0.5
1995	51	2.3	1.8	10	0.4	0.3
1996	41	1.8	1.4	18	0.8	0.5
1997	52	2.3	1.8	12	0.5	0.4
1998	43	1.9	1.4	8	0.4	0.2
1999	65	3.0	2.3	13	0.6	0.4
2000	70	3.2	2.3	19	0.9	0.5
2001	51	2.4	1.7	8	0.4	0.2
2002	59	2.7	2.0	12	0.6	0.3
2003	68	3.2	2.3	11	0.5	0.3
2004	82	3.8	2.7	16	0.7	0.4
2005	82	3.8	2.7	13	0.6	0.3
2006	86	4.0	3.0	9	0.4	0.2
2007	73	3.4	2.4	12	0.6	0.3
2008	94	4.4	3.2	15	0.7	0.4
2009	114	5.4	3.8	7	0.3	0.2
2010	96	4.5	3.2	19	0.9	0.6

*ASRW = age-standardized rate *per* 100 000 (using world standard population) ledra in

of 5.5% (95% CI, 4.4 to 6.6), with no joinpoints identified (Tables 3 and 4, Fig. 2). The age-specific incidence trends were significantly increasing in the 30-69 age groups analyzed, with the most prominent increase of EAPC (8.1%) for incidence in the youngest 30-39 age group (Table 4). The age-standardized mortality rates decreased nonsignificantly with EAPC -1.3% (95% CI, -3.5 to 1.0) (Table 4, Fig. 2). There were no significant changes in mortality trends in men in any age group (Table 4).

Histologic groups

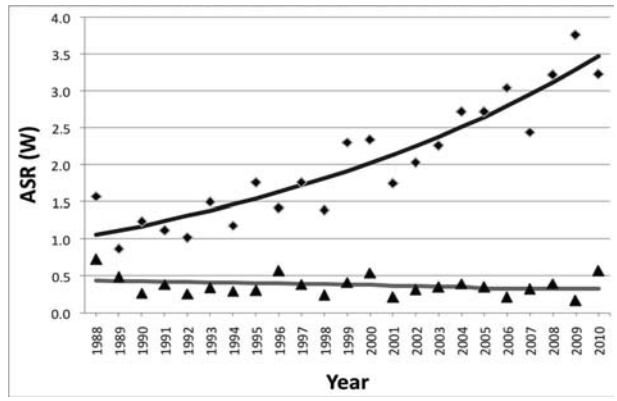
The number of new papillary carcinoma cases doubled between the first and the last three-year period

Table 4. Joinpoint analysis of age-specific and age-standardized rates of thyroid cancer incidence and mortality in Croatian men 1988–2010

Age (years)	Trend	
	years	EAPC† (%95 CI)
Incidence		
30-39	1988-2010	8.1* (5.2 to 11.0)
40-49	1988-2010	5.3* (3.0 to 7.6)
50-59	1988-2010	7.3* (5.2 to 9.5)
60-69	1988-2010	5.7* (3.3 to 8.2)
70-79	1988-2010	N/A
>80	1988-2010	N/A
Age-standardized		
overall	1988-2010	5.5* (4.4 to 6.6)
truncated (30-64)	1988-2010	6.0* (4.7 to 7.2)
Mortality		
30-39	1988-2010	N/A
40-49	1988-2010	N/A
50-59	1988-2010	N/A
60-69	1988-2010	-1.3 (-4.3 to 1.8)
70-79	1988-2010	N/A
>80	1988-2010	N/A
Age-standardized		
overall	1988-2010	-1.3 (-3.5 to 1.0)
truncated (30-64)	1988-2010	-1.0 (-4.0 to 2.0)

N/A = not applicable due to insufficient number of cases; *statistically significant trend; †EAPC = estimated annual percent change

Fig. 2. Joinpoint analysis of thyroid cancer incidence and mortality in Croatian men 1988–2010.



Rhomb = incidence; triangle = mortality; ASR(W) = age-standardized rate per 100 000 (using world standard population)

Table 5. Incidence trends of thyroid cancer according to subgroups and sex 1998-2010

1998-2010	Women	Men
	EAPC† (95% CI)	EAPC† (95% CI)
Papillary	6.7* (5.8 to 7.7)	7.9* (5.0 to 10.9)
Follicular	2.1 (-2.0 to 6.3)	-0.7 (-8.4 to 7.6)
Others	-0.7 (-5.7 to 4.5)	0.3 (-6.0 to 7.0)

*Statistically significant trend; †EAPC = estimated annual percent change

(1998-2000 and 2008-2010). The number of follicular and medullary carcinoma cases increased 1.1- and 1.6-fold, while the number of anaplastic carcinoma was unchanged. The proportion of papillary carcinoma in overall thyroid cancer rose from 81% to 87%, while the proportion of other subgroups decreased from 12.8% to 8.1% for follicular carcinoma, from 4.5% to 4.1% for medullary carcinoma, and from 1.7% to 0.9% for anaplastic carcinoma.

Joinpoint analysis of three broad histologic groups of thyroid cancer (papillary, follicular and other specified or not otherwise specified carcinomas) indicated a statistically significant incidence increase in the study period only for papillary carcinomas (Table 5). The annual incidence increase was 6.7% in women (95% CI, 5.8 to 7.7) and 7.9% in men (95% CI, 5.0 to 10.9).

Discussion

Time trends of thyroid cancer incidence and mortality were for the first time systematically analyzed in Croatia by joinpoint regression modeling that is the optimal method to detect and depict sharp changes in trends, reflecting changes in cancer prevention and care policies.

Our results indicated an increase in thyroid cancer incidence in Croatia in both sexes between 1988 and 2010, with persistent and steady decrease in mortality in women and statistically nonsignificant decrease in mortality in men. The most prominent incidence increase was observed in the 50-59 age group in women and in the youngest 30-39 age group in men.

From the 1970s, incidence rates increased in most European countries, although a decrease was recorded in some countries, such as Sweden and Norway[24]. Rising incidence trends are also observed in non-European countries, such as US and Canada[5,25]. In the last fifty years (1960-2004), mortality from thyroid cancer declined in Europe in both sexes and the falls tended to be larger in women[26].

According to the observed thyroid cancer incidence of ASR 11.4/100 000, Croatia is ranked as the fourth European country with the highest thyroid cancer incidence. Higher incidence rates than in Croatia are registered only in Lithuania (15.5/100 000), Italy (13.5/100 000) and Austria (12.4/100 000)[4]. With the observed thyroid cancer mortality of ASR 0.5/100 000, Croatia is ranked the 17th of 40 European countries[4]. The highest mortality ASR in Europe was observed in Russia (1.1/100 000), Iceland (0.8/100 000) and Lithuania (0.7/100 000)[4].

When analyzing trends by sex, we can claim that Croatia, compared to other European countries from the EUCAN database, has a high female and male thyroid incidence and moderate mortality[4]. Countries with the highest incidence rates among women are Lithuania (24.2/100 000) and Italy (18.7/100 000) and with the highest mortality rates Russia (1.3/100 000) and Latvia (0.9/100 000)[4]. Similar country order applies to men; by incidence, Croatia ranks fifth after Italy, Austria, Luxembourg and France, while by mortality of thyroid cancer in men, Croatia ranks ninth after Iceland, Russia, Cyprus, Lithuania, Slovenia, Hungary, Italy and Austria[4].

Despite various explanations in the past, recent studies suggest that the reasons for increase in the incidence are not completely understood[12] and that the cause is most likely multifactorial[27]. Liu *et al.* suggest etiologic heterogeneity between women and men in the pathogenesis of thyroid cancer[5]. The majority of authors are in favor of more intensive diagnostics as the reason for the increasing trends. Advanced medical procedures such as ultrasound and fine-needle aspiration biopsy have contributed to detection of thyroid cancer, especially smaller ones. Against these claims are results such as the increase of thyroid cancers larger than 4 cm[24,28]. Also, our results suggest that despite the incidence increase, there is no increase in thyroid cancer mortality. These findings could be explained in two ways. One is that cancer treatment in Croatia is at a high level. The second possible answer is that carcinomas, mostly microcarcinomas that make the majority of newly diagnosed thyroid cancers, are clinically nonsignificant[29]. The size of tumors could not be obtained

from the Croatian National Cancer Registry and therefore trends in tumor size were not part of our analysis. Iodine intake was also analyzed as a possible explanation for changes in thyroid cancer trends, and increase in the incidence of thyroid cancer in Croatia cannot be attributed to the increased iodine intake[30,31].

According to the data obtained, it can be concluded that the incidence increase is almost entirely due to the increase in papillary carcinoma. Similar trends are observed by other authors[5,11,12,32]. In the study by Howlader *et al*., as well as in our study, six of seven thyroid cancers were papillary carcinomas[33]. The increase of papillary carcinomas, which have better clinical outcome in comparison with other histologic subtypes of thyroid cancer, also has influenced the mortality decrease in women in Croatia.

An interesting fact was found when Croatia was compared with other countries in southeast Europe. Croatia as a country with high incidence rates is an exception, since other countries in this part of Europe have the lowest incidence rates in all Europe, EAPC <3.6/100 000[4]. More than 20 years ago, the majority of these countries were parts of former Yugoslavia and were involved in the war in the 1990s. These countries have the same geographical position, in Yugoslavia had shared similar health care system, and had similar exposure to external factors. Griniatsos *et al*. have discussed the Chernobyl accident from 1986 and depleted uranium weapons during the 1990s war on the former Yugoslavia territory as the possible factors influencing thyroid cancer trends in Greece, however, with no proven correlation[10]. All the above mentioned imposes further thoughts. If the reason for incidence increase is intensive diagnostics, does it mean that Croatia has the most optimal diagnostics, even better than some developed EU countries? If the reasons for high incidence are external factors such as Chernobyl and war, why are there such differences between geographically neighboring countries that had the same or similar exposure? Another possible explanation for the observed difference between Croatia and other countries in southeast Europe could possibly be found in cancer registries of these countries, the way they are organized and differences in data collection. These differences are striking and demand thorough investigation and further analysis.

Among European countries, there is certain regularity in mortality distribution; the highest rates are recorded in the east of Europe and these rates decrease toward countries in the west of Europe, with few exceptions[4]. Whether this is so because of better thyroid cancer treatment or earlier diagnosis in western European countries, or there are other factors, is yet to be analyzed.

In Croatia, thyroid cancer showed an incidence increase in both sexes during the 23-year study period, with a significant decrease in mortality in women and nonsignificant decrease in mortality in men. The incidence increase of thyroid cancer can be attributed to the increase of papillary carcinomas. The trends observed are similar to those in other European countries and require additional analysis to determine the factors influencing these trends.

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Sažetak

TRENDOVI U INCIDENCIJI I SMRTNOSTI KARCINOMA ŠTITNJAČE U HRVATSKOJ U RAZDOBLJU OD 1988. DO 2010. GODINE

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Cilj ovoga rada bio je opisati i protumačiti trendove incidencije i smrtnosti karcinoma štitnjače u Hrvatskoj u razdoblju od 1988. do 2010. godine, usporediti ih s trendovima u drugim zemljama te odrediti udio histoloških tipova karcinoma štitnjače i njihov utjecaj na trendove. Koristeći podatke iz Registra za rak Hrvatske i iz baze podataka Svjetske zdravstvene organizacije učinjena je regresijska analiza uz pomoć točaka spajanja za procjenu trendova incidencije i smrtnosti. Incidencija karcinoma štitnjače porasla je i kod žena i kod muškaraca u promatranom razdoblju s procijenjenim godišnjim postotkom promjene (engl. *estimated annual percent change*, EAPC) od 6,4% i 5,5%, bez identificiranih točaka spajanja. Kod žena je zabilježen značajan pad smrtnosti (EAPC -2,1%), dok se kod muškaraca smrtnost smanjila, ali statistički neznačajno (EAPC -1,3%). Statistički značajan porast incidencije zabilježen je samo kod papilarnih karcinoma s godišnjim postotkom promjene od 6,7% za žene i 7,9% za muškarce. Incidencija karcinoma štitnjače porasla je u promatranom razdoblju uz stalan i umjeren pad smrtnosti kod žena te uz statistički neznačajan pad smrtnosti kod muškaraca. Incidencija karcinoma štitnjače je porasla zbog porasta broja papilarnih karcinoma, što je također utjecalo na pad smrtnosti od karcinoma štitnjače kod žena. Zabilježeni trendovi su slični trendovima u drugim europskim zemljama i zahtijevaju dodatnu analizu svih čimbenika koji na njih utječu.

Ključne riječi: *Štitnjača, tumori – epidemiologija; Štitnjača, tumori – trendovi; Hrvatska*